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The overall objective of our research proposal is nonparametric inference of the the joint survival function $S(x_1, ..., x_d) = \Pr(X_1 > x_1, ..., X_d > x_d)$ of d (≥ 2) time-to-event variables X_1, ..., X_d, each of which is subject to interval censoring. The standard estimator of S is the generalized maximum likelihood estimator (GMLE) $\hat{S}$. However, $\hat{S}$ cannot be expressed in a closed-form expression and its statistical properties have not been studied in the multivariate case. The technical objectives of this pioneer methodological research proposal are to develop asymptotic generalized maximal likelihood (GML) inference of S and to derive efficient computational algorithms for the GML procedure. In our first year of research, we have established fundamental results regarding consistency, and asymptotic normality and efficiency under a finite assumption. The results will be useful to breast cancer researchers pursuing chemoprevention intervention trials involving multiple surrogate endpoint biomarkers, and genetic epidemiologists conducting studies on familial aggregation of breast cancer and related cancers. Moreover, we have implemented computer software packages for carrying out the asymptotic GML procedure.

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George Wong 7/31/00

PI - Signature Date

A. TABLE OF CONTENTS

B. INTRODUCTION

Interval-censored (IC) data are encountered in three areas of breast cancer research. The most common application is in clinical relapse follow-up studies in which the study endpoint is disease-free survival. When a patient relapses, it is usually known that the relapse takes place between two follow-up visits, and the exact time to relapse is unknown. In statistics, we say relapse time is interval censored. Interval censoring is also encountered in breast cancer registry studies in which information on family history of cancer is updated periodically. The Strang Breast Surveillance Program for women at increased risk for breast cancer, for instance, has enlisted over 800 women with complete pedigree information which is verified and updated continuously. Family history data such as age at diagnosis of a specific cancer, or a benign but risk-conferring condition, are obtained from each registrant at each update. Time to a cancer event, and definitely time to first detection of a benign condition, are at best known to fall in the time interval between the last update and age at diagnosis. A third but increasingly important area of application of interval censoring is in breast cancer chemoprevention experiments or prevention trials, which involve the observation of one or more surrogate endpoint biomarkers (SEB) over time. The scientific question of interest here is the estimation of time for the SEB to reach a target value, and time from cessation of intake of a chemopreventive agent to the loss of its protective effect. Unfortunately, the exact values of both these time variables are known only to lie in between two successive assay inspection times.

Let X denote a time-to-event variable with distribution $F(x) = Pr(X \leq x)$, or equivalently, survival function $S(x) = 1 - F(x)$. In interval censoring, X is not observed and is known only to lie in an observable interval (L, R). In our previous DOD funded grant, we have made fundamental contributions to both the theory of the generalized maximum likelihood (GML) estimation of S, and the computation in connection with the inference of GML estimator (GMLE) $\hat{S}$ of S. These contributions are restricted to the case of univariate interval-censored data.

Multivariate interval censoring involves $d \geq 2$ correlated X variables, each of which is subject to interval censoring. The main statistical concern here is the GML estimation of the joint survival function $S(x_1, ..., x_d) = Pr(X_1 > x_1, ..., X_d > x_d)$, and the correlations among the variables. Our interest in multivariate IC data is driven by needs arising from two related areas of breast cancer research at Strang. First, our investigators in the Strang Cancer Genetics Program want to study various patterns of familial aggregation of breast, ovarian and other forms of cancer using family history data from the Strang Breast Surveillance Program. Studies of familial early onset of breast cancer, breast-ovarian and breast-prostate associations will lead to multivariate IC data of high dimensions; therefore, a proper statistical procedure together with a feasible software to deal with such data are very much needed. Second, we are conducting a one-year chemoprevention trial of indole-3-carbinol (I3C) for breast cancer prevention. In this prevention trial we are monitoring the levels of two SEB's, a urinary estrogen metabolite ratio and a blood counterpart, both of which are subject to interval censoring. An earlier dose-ranging study of I3C conducted by Wong *et al* [1] has been published.

Statistical analysis of multivariate IC data has never been attempted. In the multivariate situation, modeling of the intercorrelated time-to-event variables and their dependency

structure will require a great deal of innovative thinking; moreover, GML computation in realistic sample sizes can be prohibitively difficult.

The overall aim of this research proposal is to develop statistical inference for multivariate interval-censored data that are encountered in breast cancer chemoprevention trials employing multiple surrogate endpoint biomarkers, and in breast cancer registry follow-up studies of familial aggregation of breast and other forms of cancer. Asymptotic generalized maximum likelihood theory will be investigated and computer software package for maximum likelihood inference and Kaplan-Meier type survival plots will be implemented.

C. BODY

Consider nonparametric estimation of the joint survival function $S(x_1, ..., x_d) = \Pr(X_1 > x_1, ..., X_d > x_d)$ of $d \geq 2$ intercorrelated time-to-event variables X_1, ..., X_d, each of which is subject to interval censoring. For ease of presentation and without any loss of generality, we shall restrict our discussion to the bivariate case $\underline{X} = (X_1, X_2)$.

Let (U_i, V_i) denote the independent random censoring interval for X_i, and (L_i, R_i) denote the observable interval-censored (IC) data for X_i defined as

$$(L_i, R_i) = \begin{cases} [0, U_i] & \text{if } X_i \leq U_i, \\ (U_i, V_i] & \text{if } U_i < X_i \leq V_i, \\ (V_i, +\infty) & \text{if } X_i > V_i, \end{cases}$$

for $i = 1, 2$. This model is called a multivariate case 2 interval censorship model.

Let B_i denote any one of $[0, U_i]$, $(U_i, V_i]$ and $(V_i, +\infty)$. Therefore, a bivariate IC data point is a rectangular region in $\mathcal{R}^2$ taking one of the nine forms in $\mathcal{B} = \{B_k \times B_l : k, l = 1, 2, 3\}$. Given a sample of size n, the observations $(L_{i1}, R_{i1}, L_{i2}, R_{i2})$ can be represented by rectangle subsets $I_i \in \mathcal{B}$, for $i = 1$, ..., n. Define a maximal intersection (MI) A of the observable rectangles I_1, ..., I_n, to be a nonempty finite intersection of the I_i's such that $A \cap I_i = \emptyset$ or A, for each i. Let A_1, ..., A_m, denote the distinct maximal intersections with respect to I_1, ..., I_n.

The generalized likelihood function of S is given by $\Lambda_n = \mu_S(I_1) \times \cdots \times \mu_S(I_n)$, where $\mu_S(\cdot)$ is the probability measure induced by S. Wong and Yu [2] show that the GMLE $\hat{S}$, which maximizes L, must assign all the probability masses s_1, ..., s_m to A_1, ..., A_m. In general, $\hat{S}$ has to be obtained iteratively. Since $\hat{S}$ is also a self-consistent estimate (SCE), we can implement the SCE algorithm by solving for $\hat{s}_1$, ..., $\hat{s}_m$ in

$$s_j = \frac{1}{n} \sum_{i=1}^{n} \frac{\delta_{ij} s_j}{\sum_{k=1}^{m} \delta_{ik} s_k},$$

$j = 1$, ..., m, where $\delta_{ij} = \mathbf{1}[A_j \subset I_i]$, $\mathbf{1}[\cdot]$ denoting the indicator function, and obtain an SCE of $S(\underline{x})$

$$\tilde{S}(\underline{x}) = \sum_{A_j \subset (x_1, +\infty) \times \cdots \times (x_d, +\infty)} \hat{s}_j.$$

With starting values $s_j^{(0)} = 1/m$ for all j, $\tilde{S}(\underline{x})$ is the GMLE at convergence.

We have implemented an algorithm to identify MI's corresponding to a set of rectangle I_1, ..., I_n, and a computer software to calculate the GMLE iteratively. The computer programs are installed in the internet sit math.binghamton.edu/ftp/pub/qyu. This completes Task 1. We have established uniform consistency of $\hat{S}$ by proving

$$\Pr\{\lim_{n\to\infty} \sup_{\underline{x} \text{ is observable}} |\hat{S}(\underline{x}) - S(\underline{x})| = 0\} = 1$$

under condition C1 (Task 2a) and under condition C2 (Task 2b):

C1. The censoring vectors (U_1, V_1) and (U_2, V_2) take on countably many values.

C2. The censoring distribution G of (U, V) is continuous, and some regularity assumptions are imposed on either S or G.

Asymptotic normality results are fundamentally important for confidence statements and hypothesis testing in data analysis. We have proved that $\sqrt{n}(\hat{S}(\underline{x}) - S(\underline{x}))/\hat{\sigma} \xrightarrow{\mathcal{D}} N(0,1)$, where $\hat{\sigma}^2$ is the inverse of the observed Fisher information number, or equivalently, $\hat{S}$ is both asymptotically normal and asymptotically efficient under condition D1 (Task 3a,b)

D1. (U_1, V_1) and (U_2, V_2) take on finitely many values, say $\underline{a_1}$, ..., $\underline{a_N}$, and $S(\underline{a_k}) > S(\underline{a_l})$, if $a_{k1} \leq a_{l1}$ and $a_{k2} \leq a_{l2}$ with at least one strict inequality, $\underline{a_k} = (a_{k1}, a_{k2})$ and $\underline{a_l} = (a_{l1}, a_{l2})$.

The above consistency and asymptotic normality results that we have accomplished in our first year of research are published in a peer-reviewed statistical journal ([2]).

D. KEY RESEARCH ACCOMPLISHMENTS IN FIRST YEAR

- We have completed task 1.

  We have developed computer software packages for computing the GMLE of the survival function $S(x_1, ..., x_d)$.

  1.a. We have developed software for identifying maximal intersections with multivariate IC data.

  1.b. We have developed software for solving self-consistent equations to obtain SCE for multivariate IC data.

- We have completed task 2.

  We have formulated a multivariate interval censorship model, called the case 2 multivariate interval censorship model. The GMLE of the distribution function is studied and its consistency and asymptotic normality are established under discrete assumptions on the censoring random vectors. Our results are published in a peer-reviewed journal (see [2]).

E. REPORTABLE OUTCOMES

- **5 published articles in journals cited in the science citation index**: [2], [3], [4], [5], [6].
- Computer programs related to Task 1 installed in math.binghamton.edu.ftp/pub/qyu.

F. CONCLUSIONS

In the first year of our DOD grant, we have successfully accomplished our research objectives stated in Tasks 1 and 2. Under the case 2 multivariate interval censorship models, we have established consistency, asymptotic normality and asymptotic efficiency of the GMLE under a finite assumption. Moreover, we have implemented computer programs for carrying out the asymptotic GML procedure.

The results which we have established will be useful to breast cancer researchers pursuing chemoprevention intervention trials involving multiple surrogate endpoints biomarkers, and genetic epidemiologists conducting studies on familial aggregation of breast cancer and related cancers.

E. REFERENCES

[1] Wong, G. Y. C., Bradlow, H. L., Sepkovic, D., Mehl, S., Mailman, J. and Osborne, M. P. (1997). A dose-ranging study of indole-3-carbinol for breast cancer prevention. *Journal of Cellular Biochemistry Supplements* 28/29, 111-116.

[2] Wong, G. Y. C. and Yu, Q. Q. (1999). Generalized MLE of a joint distribution function with multivariate interval-censored data. *J. of Multi. Anal.* 69, 155-166.

[3] Yu, Q. Q., Li, L. X. and Wong, G. Y. C. (2000). On consistency of the self-consistent estimator of survival functions with interval censored data. *Scan. J. of Statist.*, 27, 35-44.

[4] Schick, A. and Yu, Q. Q. (2000). Consistency of the GMLE with mixed case interval-censored data. *Scan. J. of Statist.*, 27, 45-55.

[5] Yu, Q. Q. and Li, L.X. (2000). Asymptotic properties of the GMLE of self-consistent estimators with doubly-censored data. *Acta Math. Sinica*, (accepted).

[6] Yu, Q. Q., Wong, G. Y. C. and Li, L. X. (2000). Asymptotic properties of self-consistent estimators with mixed interval-censored data. *Ann. Inst. Statist. Math.*, (accepted).